UNITED STATES PATENT AND TRADEMARK OFFICE

UNITED STATES DEPARTMENT OF COMMERCE
United States Patent and Trademark Office
Address: COMMISSIONER FOR PATENTS
P.O. Box 1450
Alexandria, Virginia 22313-1450
www.uspto.gov

APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
10/705,432	11/10/2003	Wojtek Auerbach	REG 784	4884

26693 7590 10/05/2005

REGENERON PHARMACEUTICALS, INC
777 OLD SAW MILL RIVER ROAD
TARRYTOWN, NY 10591

EXAMINER	
MONTANARI, DAVID A	
ART UNIT	**PAPER NUMBER**
1632	

DATE MAILED: 10/05/2005

Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary	Application No.	Applicant(s)	
	10/705,432	AUERBACH ET AL.	
	Examiner	Art Unit	
	David Montanari	1632	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☐ Responsive to communication(s) filed on _____.

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) 1-16 is/are pending in the application.

4a) Of the above claim(s) _____ is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) 1-16 is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☒ Information Disclosure Statement(s) (PTO-1449 or PTO/SB/08) Paper No(s)/Mail Date 11/10/03.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____ .
5) ☐ Notice of Informal Patent Application (PTO-152)
6) ☐ Other: _____.

DETAILED ACTION

1. Claims 1-16 are examined in the instant application

Claim Rejections - 35 USC § 112

The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

Claims 1-16 are rejected under 35 U.S.C. 112, first paragraph, because the specification, while being enabling for a method of generating drug resistant human and mouse embryonic stem (ES) cell colonies *in vitro* comprising introducing into said cells a drug resistance gene under control of a ubiquitin promoter, and a method of targeting a targeting vector *in vitro* into human and mouse ES cells comprising introducing into said cells a targeting vector comprising a drug resistance gene under control of a ubiquitin promoter, does not reasonably provide enablement for a method of generating drug resistant embryonic stem cell colonies *in vivo* comprising introducing into said cells a drug resistance gene under control of a ubiquitin promoter, and a method of targeting a targeting vector *in vivo* into ES cells comprising introducing into said cells a targeting vector comprising a drug resistance gene under control of a ubiquitin promoter. The specification does not enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the invention commensurate in scope with these claims.

Claims 1-16 are drawn to a method of generating embryonic stem (ES) cell colonies exhibiting drug resistance to a selection agent, comprising introducing into the ES cells an exogenous DNA comprising a ubiquitin promoter, and a drug resistance gene under control of

the ubiquitin promoter, wherein the ES cells are mammalian ES cells, mouse ES cells, wherein the drug resistance gene encodes neomycin phosphotransferase, hygromycin phosphotransferase, or puromycin acetyl transferase, wherein said promoter is the ubiquitin C promoter that is a human, mouse, rat, or bacterial ubiquitin C promoter, and a method of targeting a targeting vector into ES cells, comprising introducing into the ES cells a targeting vector comprising a drug resistance gene under control of a ubiquitin promoter.

While determining whether a specification is enabling, one considers whether the claimed invention provides sufficient guidance to make and use the claimed invention, if not, whether an artisan would have required undue experimentation to make and use the claimed invention and whether working examples have been provided. When determining whether a specification meets the enablement requirements, some of the factors that need to be analyzed are: the breadth of the claims, the nature of the invention, the state of the prior art, the level of one of ordinary skill, the level of predictability in the art, the amount of direction provided by the inventor, the existence of working examples, and whether the quantity of any necessary experimentation to make or use the invention based on the content of the disclosure is "undue" (In re Wands, 858 F.2d 731, 737, 8 USPQ2d 1400, 1404 (Fed. Cir. 1988)). Furthermore, USPTO does not have laboratory facilities to test if an invention will function as claimed when working examples are not disclosed in the specification, therefore, enablement issues are raised and discussed based on the state of knowledge pertinent to an art at the time of the invention, therefore skepticism raised in the enablement rejections are those raised in the art by artisans of expertise.

The breadth of the claims encompass the targeting of any ES cell in vivo with a targeting construct comprising a drug resistance gene under control of any ubiquitin promoter.

Whereas the nature of the invention is a method of generating drug resistant ES cells for selection, the art teaches that such a method would be unpredictable. The art teaches that ES cells other than mouse or human in origin have been isolated, however only mouse and chicken ES cells have proven to be capable of colonizing the germline (aside from human) (Wobus et al. 2005, Physiol. Rev. Vol. 85, pgs. 635-678). The art continues that the random introduction of transgenes into ES cells, i.e. drug resistant genes, tend to be progressively silenced, resulting in mosaic expression, or complete silencing (Wobus, pg. 643, col. 2). The art continues that ES cells have been established for rabbits, rat, Syrian hamster, mink, pig, cattle, sheep, rhesus monkey, common marmoset, medakafish, and zebrafish (Prelle et al., Cell Tissues Organs, 1999, Vol. 165, pgs. 220-236, Table 2). However, the art teaches that each of said animals has inherent difficulties that make genetic manipulation difficult and unpredictable wherein the ES cell could be used for further experimentation (Prelle, pgs. 222-229).

The working examples provided by the specification teach targeting vectors comprising the ubiquitin promoter and the PGK promoter were used to drive the expression of a drug resistance gene in mouse ES cells (pg. 10, Example 1). The specification continues to teach that comparison between ubiquitin and the PGK promoter resulted in a significant increase in % targeting of mouse ES cells compared between the two said promoters (pg. 11, Table 2). However, the specification has failed to teach a method of generating any drug resistant ES cell other than mouse or human. Further the specification is has described only the *in vitro* administration of a targeting vector. No guidance by the specification is provided to the skilled artisan that would enable the *in vivo* administration of a targeting vector to generate ES cell colonies with drug resistance.

Therefore, in view of the breadth of the claims and the lack of guidance provided by the specification as well as the unpredictability of the art, the claimed invention is not enabled for its full breadth and limiting the scope of the claimed invention to a method of generating drug resistant human and mouse embryonic stem (ES) cell colonies *in vitro* comprising introducing into said cells a drug resistance gene under control of a ubiquitin promoter, and a method of targeting a targeting vector *in vitro* into human and mouse ES cells comprising introducing into said cells a targeting vector comprising a drug resistance gene under control of a ubiquitin promoter is proper.

Claim Rejections - 35 USC § 103

The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

Claims 1-16 are rejected under 35 U.S.C. 103(a) as being unpatentable over Ghazizadeh et al. (J. of Investigative Dermatology, 1998, Vol. 111, pgs. 492-496) in view of Gill et al. (Gene Therapy, 2001, Vol. 8, pgs. 1539-1546).

Claims 1-16 are drawn to a method of generating embryonic stem (ES) cell colonies exhibiting drug resistance to a selection agent, comprising introducing into the ES cells an exogenous DNA comprising a ubiquitin promoter, and a drug resistance gene under control of the ubiquitin promoter, wherein the ES cells are mammalian ES cells, mouse ES cells, wherein the drug resistance gene encodes neomycin phosphotransferase, hygromycin phosphotransferase,

or puromycin acetyl transferase, wherein said promoter is the ubiquitin C promoter that is a human, mouse, rat, or bacterial ubiquitin C promoter, and a method of targeting a targeting vector into ES cells, comprising introducing into the ES cells a targeting vector comprising a drug resistance gene under control of a ubiquitin promoter.

Ghazizadeh et al. teach using a retrovirus vector comprising the lacZ gene and the neomycin phosphotransferase gene the to select non-transformed porcine keratinocytes using the drug G418 to select cells which are not expressing neomycin phosphotransferase (pg. 493, col. 1 parag. 3).

Gill et al. teach using the human ubiquitin C promoter results in significant increases in transgene expression compared to other promoters such as CMV (pg. 1540, col. 1 parag. 1). Gill continues that using the ubiquitin C promoter driving a luciferase reporter gene resulted in observable expression for up to 6-months following gene delivery in mouse lung tissue (pg. 1542, col. 1 parag. 1 bridge col. 2, and Fig. 7).

Thus the ordinary artisan would have been motivated by the teachings of Ghazizadeh and Gill to modify the method of Ghazizadeh in view of the method taught by Gill to generate ES cell colonies exhibiting drug resistance by using any drug resistant gene to a selection agent. Motivation is provided by Ghazizadeh teaching that drug resistance genes are used to select cells that express the transgene of interest. Further motivation is provided by Gill teaching that use of the human ubiquitin C promoter is beneficial compared to other promoters due to it's increased transgene expression that can be as long as 6-months following gene delivery. Thus the cited art provides the requisite teachings and motivation to make and us the claimed invention.

No claims are allowed.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to David Montanari whose telephone number is 1-571-272-3108. The examiner can normally be reached on M-F 9-5:30.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Ram Shukla can be reached on 1-571-272-0735. The fax phone number for the organization where this application or proceeding is assigned is 571-273-8300.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free).

David A. Montanari, PhD

RAM R. SHUKLA, PH.D.
SUPERVISORY PATENT EXAMINER